CLAIMS

What is claimed is:

1. A Class II Major Histocompatibility Complex fusion protein comprising a fusion of, toward the N-terminus, at least an MHC Class II binding domain of an MHC Class II α chain and, toward the C-terminus, a dimerization domain.

2. A Class II Major Histocompatibility Complex fusion protein as in claim 1 wherein said MHC Class II binding domain comprises an extracellular domain of an MHC Class II α chain.

3. A Class II Major Histocompatibility Complex fusion protein as in claim 2 wherein said extracellular domain comprises residues 5-180 of an MHC Class II α chain.

4. A Class II Major Histocompatibility Complex fusion protein as in claim 2 wherein said extracellular domain comprises residues 5-200 of an MHC Class II α chain.

5. A Class II Major Histocompatibility Complex fusion protein as in claim 2 wherein said extracellular domain comprises residues 5-190 of an MHC Class II α chain.

6. A Class II Major Histocompatibility Complex fusion protein as in claim 1 wherein said MHC Class II α chain is selected from the group consisting of HLA-DR1, HLA-DR2, HLA-DR4, HLA-DQ1, HLA-DQ2 and HLA-DQ8 α chains.

7. A Class II Major Histocompatibility Complex fusion protein as in claim 1 wherein said MHC Class II α chain is encoded by an HLA allele selected from the group consisting of DRA*0101, DRA*0102, DQA1*0301 and DQA1*0501 alleles.

8. A Class II Major Histocompatibility Complex fusion protein comprising a fusion of, toward the N-terminus, at least an MHC Class II binding domain of an MHC Class II β chain and, toward the C-terminus, a dimerization domain.

9. A Class II Major Histocompatibility Complex fusion protein as in claim 8 wherein said MHC Class II binding domain comprises an extracellular domain of an MHC Class II β chain.

10. A Class II Major Histocompatibility Complex fusion protein as in claim 9 wherein said extracellular domain comprises residues 5-185 of an MHC Class II β chain.

11. A Class II Major Histocompatibility Complex fusion protein as in claim 9 wherein said extracellular domain comprises residues 5-205 of an MHC Class II β chain.

12. A Class II Major Histocompatibility Complex fusion protein as in claim 9 wherein said extracellular domain comprises residues 5-195 of an MHC Class II β chain.

13. A Class II Major Histocompatibility Complex fusion protein as in claim 8 wherein said MHC Class II β chain is selected from the group consisting of HLA-DR1, HLA-DR2, HLA-DR4, HLA-DQ1, HLA-DQ2 and HLA-DQ8 β chains.

14. A Class II Major Histocompatibility Complex fusion protein as in claim 13 wherein said MHC Class II β chain is encoded by an allele selected from the group consisting of DRB1*01, DRB1*15, DRB1*16, DRB5*01, DQB1*03 and DQB1*02 alleles.

15. A Class II Major Histocompatibility Complex fusion protein as in any one of claims 1-14 wherein

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said dimerization domain is a coiled-coil dimerization domain.

16. A Class II Major Histocompatibility Complex fusion protein as in claim 15 wherein said dimerization domain is a leucine zipper domain.

17. A Class II Major Histocompatibility Complex fusion protein as in claim 16 wherein said leucine zipper domain comprises at least four leucine heptads.

18. A Class II Major Histocompatibility Complex fusion protein as in claim 16 wherein said leucine zipper domain is selected from the group consisting of a Fos and a Jun leucine zipper domain.

19. A Class II Major Histocompatibility Complex fusion protein as in any one of claims 1-14 wherein

said dimerization domain is an immunoglobulin Fab constant domain.

20. A Class II Major Histocompatibility Complex fusion protein as in claim 19 wherein said immunoglobulin Fab constant domain is an immunoglobulin heavy chain C_H1 constant region.

21. A Class II Major Histocompatibility Complex fusion protein as in claim 19 wherein said immunoglobulin Fab constant domain is an immunoglobulin light chain constant region.

22. A Class II Major Histocompatibility Complex fusion protein as in any one of claims 1-14 further comprising

A flexible molecular linker interposed between and covalently joining said MHC Class II chain and said dimerization domain.

23. A Class II Major Histocompatibility Complex fusion protein as in claim 22 wherein said flexible molecular linker comprises a peptide sequence of 1-15 amino acid residues.

24. A Class II Major Histocompatibility Complex fusion protein as in claim 23 wherein said flexible molecular linker comprises a peptide sequence of 5-7 amino acid residues.

25. A Class II Major Histocompatibility Complex fusion protein as in claim 23 wherein a majority of said amino acid residues are selected from the group consisting of alanine, glycine, serine, leucine, isoleucine, and valine residues.

26. A Class II Major Histocompatibility Complex fusion protein as in any one of claims 1-7 further comprising

an MHC Class II binding peptide covalently joined to the N-terminus of said MHC Class II α chain,

wherein said binding peptide is capable of selectively binding to an MHC Class II molecule including said α chain and an MHC Class II β chain to form an MHC/peptide complex.

27. A Class II Major Histocompatibility Complex fusion protein as in any one of claims 8-14 further comprising

an MHC Class II binding peptide covalently joined to the N-terminus of said MHC Class II β chain,

wherein said binding peptide is capable of selectively binding to an MHC Class II molecule including said β chain and an MHC Class II α chain to form an MHC/peptide complex.

28. A Class II Major Histocompatibility Complex fusion protein as in claim 27 wherein

said MHC Class II molecule is an HLA-DR2 molecule and said binding peptide is selected from the group consisting of residues 85-99, 84-102 and 148-162 of human myelin basic protein.

29. A Class II Major Histocompatibility Complex fusion protein as in claim 27 wherein said MHC Class II molecule is an HLA-DR4 molecule and said binding peptide is selected from the group consisting of residues 78-93, 97-111, 190-204, 206-220, 251-265, 512-526 and 762-786 of the human desmoglein 3 protein.

30. A Class II Major Histocompatibility Complex fusion protein as in claim 27 wherein said MHC Class II molecule is an HLA-DQ1 molecule and said binding peptide is selected from the group consisting of residues 78-93, 97-111, 190-204, 206-220, 251-265, 512-526 and 762-786 of the human desmoglein 3 protein.

31. A Class II Major Histocompatibility Complex fusion protein as in any one of claims 26-30 further comprising

A flexible molecular linker interposed between and covalently joining said MHC Class II chain and said MHC binding peptide.

32. A Class II Major Histocompatibility Complex fusion protein as in claim 31 wherein said flexible molecular linker comprises a peptide sequence of 10-20 amino acid residues.

33. A Class II Major Histocompatibility Complex fusion protein as in claim 32 wherein said flexible molecular linker comprises a peptide sequence of 12-18 amino acid residues.

34. A Class II Major Histocompatibility Complex fusion protein as in claim 32 wherein a majority of said amino acid residues are selected from the group consisting of alanine, glycine, serine, leucine, isoleucine, and valine residues.

35. A Class II Major Histocompatibility Complex fusion protein comprising a heterodimer of a first polypeptide chain and a second polypeptide chain;

wherein said first polypeptide chain comprises a fusion of, toward the N-terminus, at least an extracellular domain of an MHC Class II α chain and, toward the C-terminus, a first dimerization domain;

wherein said second polypeptide chain comprises a fusion of, toward the N-terminus, at least an extracellular domain of an MHC Class II β chain and, toward the C-terminus, a second dimerization domain; and

wherein said first dimerization domain and said second dimerization domain associate in solution at physiological conditions to form a heterodimer capable of selectively binding an MHC binding peptide.

36. A Class II Major Histocompatibility Complex fusion protein comprising a heterodimer of a first polypeptide chain and a second polypeptide chain;

wherein said first polypeptide chain comprises a fusion of, toward the N-terminus, at least an extracellular domain of an MHC Class II α chain and, toward the C-terminus, an immunoglobulin heavy chain C_H1 constant region;

wherein said second polypeptide chain comprises a fusion of, toward the N-terminus, at least an extracellular domain of an MHC Class II β chain and, toward the C-terminus, an immunoglobulin light chain constant region; and

wherein said immunoglobulin heavy chain C_H1 constant region and said immunoglobulin light chain constant region dimerize in solution at physiological conditions to form a heterodimer capable of selectively binding an MHC binding peptide.

37. A Class II Major Histocompatibility Complex fusion protein comprising a heterodimer of a first polypeptide chain and a second polypeptide chain;

wherein said first polypeptide chain comprises a fusion of, toward the N-terminus, at least an extracellular domain of an MHC Class II α chain and, toward the C-terminus, an immunoglobulin light chain constant region;

wherein said second polypeptide chain comprises a fusion of, toward the N-terminus, at least an extracellular domain of an MHC Class II β chain and, toward the C-terminus, an immunoglobulin heavy chain C_H1 constant region; and

wherein said immunoglobulin heavy chain C_H1 constant region and said immunoglobulin light chain constant region dimerize in solution at physiological conditions to form a heterodimer capable of selectively binding an MHC binding peptide.

38. A Class II Major Histocompatibility Complex fusion protein as in any one of claims 36-37 further comprising

an immunoglobulin Fc region covalently joined to said immunoglobulin heavy chain C_H1 constant region.

39. A Class II Major Histocompatibility Complex fusion protein as in claim 38 wherein

said immunoglobulin Fc region is selected from the group consisting of IgE and IgM Fc regions.

40. A Class II Major Histocompatibility Complex fusion protein as in claim 39 further comprising

a flexible molecular linker interposed between and covalently joining said immunoglobulin heavy chain C_H1 constant region and immunoglobulin Fc region.

41. A Class II Major Histocompatibility Complex fusion protein as in claim 38 wherein

said immunoglobulin Fc region is selected from the group consisting of IgA, IgD and IgG Fc regions.

42. A Class II Major Histocompatibility Complex fusion protein as in claim 41 further comprising

a flexible molecular linker interposed between and covalently joining said immunoglobulin heavy chain C_H1 constant region and immunoglobulin Fc region.

43. A Class II Major Histocompatibility Complex fusion protein as in claim 42 wherein said flexible molecular linker is an immunoglobulin hinge region.

44. A multivalent Class II Major Histocompatibility Complex fusion protein comprising two Class II Major Histocompatibility Complex fusion proteins of any one of claims 38-43 wherein,

said Fc regions are covalently joined by at least one disulfide bond.

45. A multivalent Class II Major Histocompatibility Complex fusion protein comprising five pairs of Class II Major Histocompatibility Complex fusion proteins of any one of claims 38-43 wherein,

said Fc regions are IgM regions, each said pair is covalently joined by at least one disulfide bond between Fc regions of said pair, and said five pairs are covalently joined by disulfide bridges to form a ring structure such that each adjacent pair in said ring is joined by at least one disulfide bond.

46. A Class II Major Histocompatibility Complex fusion protein as in any one of claims 1-14 further comprising

an N-terminal secretory signal sequence covalently joined to the N-terminus of said fusion protein.

47. A Class II Major Histocompatibility Complex fusion protein as in claim 46 wherein said secretory signal sequence comprises a yeast α-mating factor secretion signal.

48. A Class II Major Histocompatibility Complex fusion protein as in claim 46 wherein

said secretory signal sequence comprises a human MHC Class II protein secretion signal.

49. A multimeric Major Histocompatibility Complex binding domain conjugate comprising a carrier and a multiplicity of MHC binding domains conjugated thereto.

50. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

about 5 to about 500 MHC binding domains are conjugated to said carrier.

51. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

about 10 to about 200 MHC binding domains are conjugated to said carrier.

52. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

about 20 to about 100 MHC binding domains are conjugated to said carrier.

53. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier defines a minimal surface and said MHC binding domains are present at an average density of about 4 x 10^{-3} to 20 MHC binding domains/nm^2 on said surface.

54. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier defines a minimal surface and said MHC binding domains are present at an average density of about 4 x 10^{-2} to 20 MHC binding domains/nm^2 on said surface.

55. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier defines a minimal surface and said MHC binding domains are present at an average density of about 0.4 to 20 MHC binding domains/nm^2 on said surface.

56. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier has a maximum diameter of about 5 to about 1000 nm.

57. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier has a maximum diameter of about 5 to about 500 nm.

58. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier has a maximum diameter of about 5 to about 100 nm.

59. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier weighs about 100 kDa to about 10,000 kDa.

60. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier weighs about 100 kDa to about 5,000 kDa.

61. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier weighs about 100 kDa to about 1,000 kDa.

62. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier weighs about 100 kDa to about 500 kDa.

63. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said conjugate weighs about 400 kDa to about 10,000 kDa.

64. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said conjugate weighs about 400 kDa to about 5,000 kDa.

65. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said conjugate weighs about 400 kDa to about 1,000 kDa.

66. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said conjugate weighs about 400 kDa to about 500 kDa.

67. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier is particulate.

68. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier is biodegradable.

69. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier is non-immunogenic.

70. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier is a branched polymer.

71. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier has a net negative charge.

72. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier has no net charge.

73. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier is fluorescently labeled.

74. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier is covalently bound to said MHC binding domains.

75. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier is non-covalently bound to said MHC binding domains.

76. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier is a substantially spherical bead.

77. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 76 wherein

said bead is porous.

78. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 76 wherein

said bead comprises a material selected from the group consisting of glass, silica, polyesters of hydroxy carboxylic acids, polyanhydrides of dicarboxylic acids, or copolymers of hydroxy carboxylic acids and dicarboxylic acids.

79. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein

said carrier comprises a branched polymer.

80. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 79 wherein

said branched polymer is a dendrimer.

81. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 80 wherein

said dendrimer defines a minimal surface; and wherein

said surface has a net neutral or net negative charge.

82. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 80 wherein

said dendrimer comprises a material selected from the group consisting of a polyamidoamine, a polyamidoalcohol, a polyalkyleneimine, a polyalkylene, a polyether, a polythioether, a polyphosphonium, a polysiloxane, a polyamide, and a polyaryl polymer.

83. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49 wherein said carrier is a liposome.

84. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 83 wherein

said liposome comprises a material selected from the group consisting of phosphatidyl choline, phosphatidyl serine, phosphatidyl inositol, phosphatidyl glycerol, phosphatidyl ethanolamine, phosphatidic acid, dicetyl phosphate, monosialoganglioside, polyethylene glycol, stearyl amine, ovolecithin and cholesterol.

85. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 49, further comprising

a multiplicity of MHC binding peptides bound to said MHC binding domains,

wherein said MHC binding peptides specifically bind said MHC binding domains under physiological conditions.

86. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 85 wherein

said MHC binding peptides are covalently bound to said MHC binding domains.

87. A multimeric Major Histocompatibility Complex binding domain conjugate as in claim 85 wherein

said MHC binding peptides are non-covalently bound to said MHC binding domains.

88. A multimeric Major Histocompatibility Complex binding domain conjugate as in any one of claims 49-87 wherein

each MHC binding domain comprises a heterodimer of at least the peptide binding domain of an MHC Class I α chain and an MHC Class I β chain.

89. A multimeric Major Histocompatibility Complex binding domain conjugate as in any one of claims 49-87 wherein

each MHC binding domain comprises a heterodimer of at least the peptide binding domain of an MHC Class II α chain and an MHC Class II β chain.

90. A multimeric Major Histocompatibility Complex binding domain conjugate as in any one of claims 49-87 wherein

wherein each MHC binding domain comprises a monovalent or multivalent MHC binding domain fusion protein.

91. A method for detecting T cells having a defined MHC/peptide complex specificity comprising

providing a monovalent, multivalent or multimeric Major Histocompatibility Complex fusion protein or conjugate of any one of claims 35-90 comprising said defined MHC/peptide complex;

contacting a population of T cells with said fusion protein or conjugate; and

detecting the presence or absence of binding of said fusion protein or conjugate and T cells in said population.

92. A method as in claim 91 further comprising

isolating T cells reactive with said defined MHC/peptide complex from said population of T cells.

93. A method as in claim 92 wherein

said isolation is by means of fluorescence activated cell sorting.

94. A method of conferring to a subject adoptive immunity to a defined MHC/peptide complex comprising

providing a monovalent, multivalent or multimeric Major Histocompatibility Complex fusion protein or conjugate of any one of claims 35-90 comprising said defined MHC/peptide complex;

contacting a population of T cells with said fusion protein or conjugate;

isolating T cells reactive with said defined MHC/peptide complex from said population of T cells; and

administering said isolated T cells to said subject to provide adoptive immunity.

95. A method for stimulating or activating T cells reactive to a defined MHC/peptide complex comprising

providing a monovalent, multivalent or multimeric Major Histocompatibility Complex fusion protein or conjugate of any one of claims 35-90 comprising said defined MHC/peptide-complex; and

contacting a population of T cells with an immunogenic amount of said fusion protein or conjugate.

96. A method as in claim 95 wherein

said fusion protein or conjugate is contacted with said population of T cells <u>in vivo</u> in a human subject; and

wherein said MHC fusion protein or conjugate comprises an MHC binding domain which is syngeneic to said subject.

97. A method for selectively killing T cells reactive to a defined MHC/peptide complex comprising

providing a monovalent, multivalent or multimeric Major Histocompatibility Complex fusion protein or conjugate of any one of claims 35-90 comprising said defined MHC/peptide-complex; and

contacting a population of T cells with said fusion protein or conjugate; wherein

said fusion protein or conjugate comprises a domain of an immunoglobulin effective to activate a complement system and cause said complement system to kill said T cells.

98. A method for selectively killing T cells reactive to a defined MHC/peptide complex comprising

providing a monovalent, multivalent or multimeric Major Histocompatibility Complex fusion protein or conjugate of any one of claims 35-90 comprising said defined MHC/peptide-complex; and

contacting a population of T cells with said fusion protein or conjugate; wherein

said fusion protein or conjugate comprises a cytotoxic substance associated with said fusion protein or conjugate and capable of killing T cells to which said fusion protein or conjugate selectively binds.

99. A method for tolerizing a human subject to a defined MHC/peptide complex comprising

providing a monovalent, multivalent or multimeric Major Histocompatibility Complex fusion protein or conjugate of any one of claims 35-90 comprising said defined MHC/peptide-complex; and

administering to said subject an amount of said fusion protein or conjugate effective to induce tolerization to said MHC/peptide complex.

100. A method as in claim 99 wherein

said MHC fusion protein or conjugate comprises an MHC binding domain which is syngeneic to said subject.

101. A method as in claim 99 wherein

said MHC fusion protein or conjugate comprises an MHC binding domain which is allogeneic to said subject.

102. An isolated nucleic acid encoding an MHC binding domain fusion protein of any one of claims 1-45.

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